Chapter 7
Physiology of High/Fast Transporters

R.T. Krediet

Patients on peritoneal dialysis have large interindividual differences in the velocity of solute equilibration between plasma and the dialysate [1]. In an attempt to standardize assessment of this variability, Twardowski et al. developed the peritoneal equilibration test (PET) [2]. In the PET solute transport after a standardized dwell of 4 h is expressed as the dialyse/plasma (D/P) concentration ratio of various solutes. D/P creatinine had a mean value of 0.65, but it ranged from 0.34 to 1.03 [3]. A similar range was reported in another study using the PET [4]. Based on D/P creatinine, patients have been divided into four transport categories: low, low average, high average, and high [3]. This categorization was based on the mean value and the standard deviation (SD). Low is less than 1 SD, low average is between the mean and –1 SD, low average is between the mean and +1 SD, and high is above 1 SD. The cut-off levels are: <0.50 for low, 0.50–0.65 for low average, 0.65–0.81 for high average, and >0.81 for high transporters. About 10% of prevalent PD patients can be classified as high transporters [5].

It should be appreciated that the net mass transfer of a solute is not only dependent on its D/P ratio, but also on the amount of drained dialysate: the peritoneal clearance is calculated as (D/P) × the drained volume. For solutes that are in (near) equilibrium, the D/P ratio approaches 1. In this situation the peritoneal clearance is almost exclusively determined by the drained volume. This is especially relevant for high transporters. These patients have a rapid disappearance of the glucose-induced osmotic gradient, caused by a high glucose absorption rate. It is not just a theoretical consideration: high transporters had a higher absorption of glucose after a dwell of 6 h, but a smaller intraperitoneal volume, while the removal of urea creatinine, sodium, and potassium was significantly lower than in the other transport categories [6]. A more detailed analysis of sodium kinetics showed that, irrespective of transport status, 69% of sodium transport is by convection, but that the high transporters had a significantly higher absorbed and lower removed sodium mass [7]. Therefore, the terms *high* and *low transport* are confusing. Patients who show a rapid equilibration could better be labeled fast transporters. Similarly the term *low* should be replaced by *slow*.

Fast Transport Status and Prognosis

The determination of peritoneal transport status was originally used to give recommendations on the dialysis prescription. For instance, the proposed treatment for fast transporters was either nightly intermittent peritoneal dialysis or daily ambulatory peritoneal dialysis [8]. In both modalities a long dwell is avoided to minimize absorption of the dialysis solution, and thereby trying to avoid the development of overhydration.

Wu et al. were the first to describe a higher drop-out rate in fast transporters when compared to other transport categories [9]. In 1998, two papers were published that reported a decreased survival for fast transporters [6, 10]. In a study from Sweden, prevalent continuous ambulatory peritoneal dialysis (CAPD) patients had a 2-year patient survival of 64%, which was significantly lower than the survival for the other transport categories. This effect was independent of age, gender, height and urine production. Diastolic blood pressure and bodyweight were higher in the fast transporters. All the deaths among the fast transporters were caused by cardiovascular diseases. These data suggest that overhydration may have been important. In the Canada-USA (CANUSA) study, performed in more than 600 incident CAPD patients, a PET was performed at enrollment [10]. No difference among the groups was found for patient survival, but fast transporters had a lower 2-year technique survival and a lower combined patient and technique survival. Fast transporters were older, more often male, and more often had diabetes mellitus and a lower serum albumin concentration. However, their nutritional status was not different from that of the other transport

R.T. Krediet (✉)
Academic Medical Center University of Amsterdam, Amsterdam, The Netherlands
e-mail: c.n.deboer@amc.uva.nl

R. Khanna, R.T. Krediet (eds.), *Nolph and Gokal's Textbook of Peritoneal Dialysis*,
DOI 10.1007/978-0-387-78939-2_7, © Springer Science+Business Media, LLC 2009

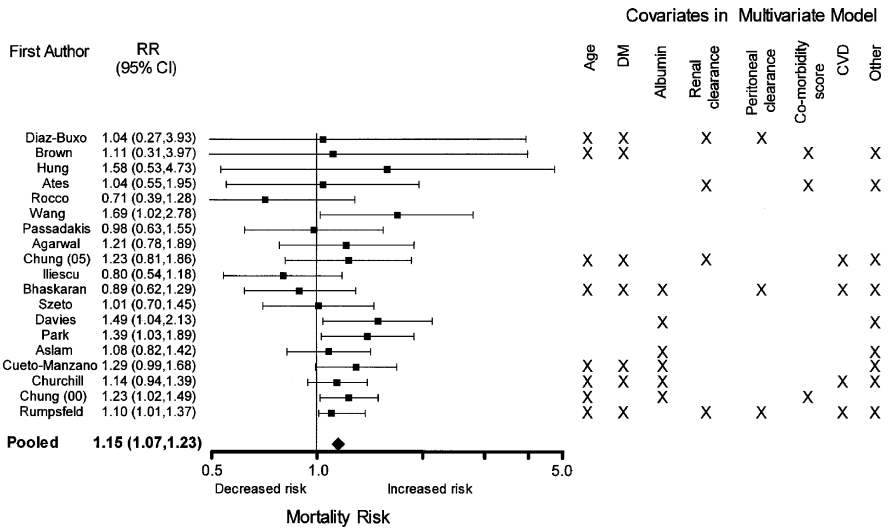

Fig. 7.1 Results of a meta-analysis on the mortality risk of patients with a fast peritoneal transport status. Taken from reference [28] (Brimble KS et al. Meta-analysis: peritoneal membrane transport mortality and technique failure in peritoneal dialysis. J Am Soc Nephrol 2006; 17: 2591–2598) with permission of the first author and of Lippincott, Williams and Wilkins

groups. Although residual renal function tended to be better in fast transporters, this was not significant. Fast transporters had a higher peritoneal creatinine clearance, a lower PET drain volume and a Kt/V_{urea} of 1.58/week compared to an average value of 1.68/week for the other transport categories. The cause of death was vascular in 73% of all patients. Taken together these data from the CANUSA study also suggest volume overload due to impaired peritoneal ultrafiltration as an important cause for the decreased patient and technique survival in fast transporters.

A large number of studies on mortality in fast transport patients has been published since then [11–27]. Among the 19 studies that assessed patient survival, five reported an increased mortality, while the other 14 showed no significant effect of peritoneal transport status. A recently published meta-analysis [28] done in 6,654 incident and prevalent PD patients showed a statistically significant overall increased relative risk of death in fast transporters of 1.15 (Fig. 7.1). A number of remarks can be made, however: 1) The majority of patients comes from one study [26]. 2) Four out of five studies showing a significant effect were done in CAPD patients [7, 12, 21, 25]. The fifth study, that is the large one from Australia/New Zealand, only found an effect in CAPD patients, not in those treated with APD [26]. In the two studies performed exclusively in APD patients, no effect of peritoneal transport status was present [14, 27]. 3) With the exception of the study by Brown et al. in APD patients [27], no study included patients in whom icodextrin was used for the long dwell. 4) A relative risk of 1.15, as reported in the meta-analysis, means that the chance of death is increased with 15%. Given a death rate in PD patients of about 15% per year, it means that the number of patients that die in 1,000 patient years will increase from 150 to 173. For comparison, the relative risk of death for start with hemodialysis compared to peritoneal dialysis is 1.59 in the United Kingdom [29], 1.16 in Denmark [30], and 2.33 in The Netherlands [31].

It can be concluded that the relationship between a fast peritoneal transport status and excess mortality has only been established in patients on CAPD treated with conventional PD solutions. The excess mortality is about 15%.

Physiology of Fast Transport Status

Diffusion through the so-called small pores is the most important transport mechanism for low molecular weight solutes that accumulate due to kidney failure. The rate of diffusion is determined by the product of the mass transfer area coefficient (MTAC, the maximum theoretical clearance by diffusion at time zero) and the concentration gradient between plasma and dialysate. Plotting MTACs of various low molecular weight solutes versus their free diffusion coefficient in water shows the presence of a power relationship between them [32]. It means that the relationship is linear when plotted on a double logarithmic scale. The slope of the regression line obtained when doing this for low molecular weight solutes was 1.24, which is close to 1.0. This is the expected value when the relationships between the magnitude of MTACs would only have been dependent of free diffusion. Consequently it is unlikely that the peritoneal membrane offers a size-selective hindrance to the transport of low molecular weight solutes. It implies that the MTACs or D/P ratios are mainly dependent on the number of perfused peritoneal microvessels, that is the vascular peritoneal surface area. This is discussed in more detail in Chapter 6.

The presence of a fast transport status reflects the presence of a large vascular peritoneal surface area. This area is not a statistical, but a dynamic property, because it is not only dependent on the number of microvessels but also on the number of perfused microvessels. The former is the anatomic surface area, the latter is often referred to as the effective peritoneal surface area. As discussed in Chapter 6, many vasoactive substances can influence the effective peritoneal surface area.

Types of Fast Transport Status

Inherent Fast Transporters

The prevalence of a fast transport status in new PD patients differs widely. Values of 7% [20] and of 29% [33] have been reported. In most studies an inherent fast transport status was present in 15–17% of the patients [10, 16, 34]. The last study comprised 523 incident PD patients with a fast transport status. Multivariate analysis revealed that this condition was associated with higher age, Maori/Pacific Islands racial origin, a BMI exceeding 25 kg/m^2, but not with co-morbidity. Male gender and the presence of diabetes mellitus were associated with a fast transport status in the CANUSA study [10]. A study from Korea confirmed that inherent fast transporters had a higher proportion of men, but – in contrast with the study from Australia/New Zealand – also a higher proportion of patients with co-morbid diseases and a lower initial serum albumin concentration [16].

Peritoneal transport status is a refection of the peritoneal vascular surface area, which can be influenced by vasoactive substances (see above). Besides urea and creatinine, the concentrations of which are determined by peritoneal transport, many substances can be detected in peritoneal effluent of PD patients that are locally produced or released. These include interleukin-6 (IL-6) [35, 36], vascular endothelial growth factor (VEGF) [37], and the mesothelial cell mass marker cancer antigen 125 (CA 125) [38]. Cross-sectional analyses in prevalent PD patients have shown significantly higher plasma and dialysate concentrations of IL-6 and VEGF in fast/fast average transporters than in slow/slow average ones [39]. Also, a strong correlation is present between the MTAC creatinine and effluent VEGF attributed to local production [37]. However, studies from Portugal in incident patients found no correlation between D/P creatinine and effluent or serum IL-6 [40]. Also, no differences were present between fast/fast average and slow/slow average transporters for serum VEGF, serum IL-6, and effluent IL-6. Only effluent VEGF was significantly higher in the fast/fast average transporters [41]. A similar finding was reported was reported in a study from The Netherlands [42]. These findings contrast those of a study from Sweden, in which a correlation was found between D/P creatinine at baseline and plasma dialysate IL-6 [43]. Population differences in inflammation may explain these differences. The average serum C-reactive protein (CRP) concentrations were 6 mg/L in the study from Portugal [41], 5 mg/L in the study from The Netherlands, in which patients with diabetes mellitus were excluded [42], and 15 mg/L in the study from Sweden [43].

Cultured mesothelial cells are able to produce various cytokines, chemokines, and prostaglandins, some of which are vasoactive [reviewed in ref. 44]. These include IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1), but not tumor necrosis factor (TNF)α, the concentration of which in peritoneal effluent of uninfected patients is dependent on diffusion from the circulation [45]. The in vitro production of the above substances is especially marked after stimulation, for instance with TNFα. In contrast, VEGF is spontaneously produced in large quantities by ex vivo cultured peritoneal mesothelial cells from PD patients [46]. Also, CA 125 is constitutively released by mesothelial cells. This release is not influenced by stimulation with cytokines [47].

Based on these data, it can be hypothesized that the magnitude of the mesothelial cell mass is indirectly involved in the regulation of the effective vascular surface area. Old data in cross-sectional studies on relationships between effluent CA 125 and peritoneal transport are equivocal. Some reported a positive correlation with D/P creatinine [48], while others were unable to establish this [49]. The discrepancy might be due to differences in the duration of peritoneal dialysis. As illustrated in Fig. 7.2, a correlation between effluent CA 125 and peritoneal solute transport is only present during the first two years on peritoneal dialysis (unpublished data). Especially in incident patients correlations are present between patients solute transport, effluent CA 125, and effluent VEGF [40–42]. By using a linear regression analysis to analyze the relationship between MTAC creatinine and effluent CA 125 in incident patients it was shown that this was not influenced by age, gender, and serum concentrations of acute phase proteins [42]. However, it was weakened when effluent VEGF was added to the model, but not when this was done for effluent IL-6 [42]. These data suggest that CA 125 in new PD patients is an independent determinant of the MTAC creatinine and that its effect is partly mediated by locally produced VEGF, presumably from mesothelial cells.

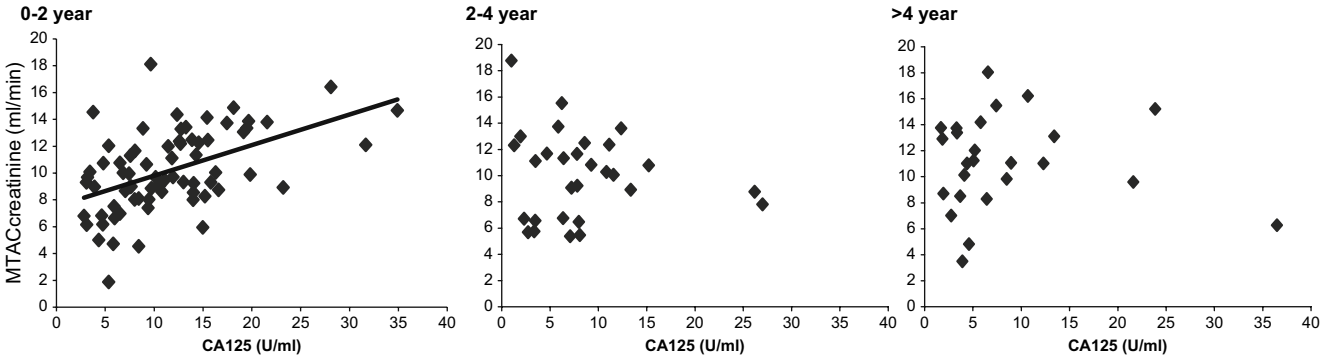

Fig. 7.2 Relationship between effluent CA 125 and the MTAC creatinine according to the duration of peritoneal dialysis. Only during the first 2 years a relationship is present

Table 7.1 Differences between the two types of an inherent fast transport status

Inherent fast transporters		
	Associated with co-morbidity	Associated with CA 125
Vascular surface area increase	Effective/anatomic	Effective
Cause	Inflammation	Vasoactive hormones produced by mesothelial cells
Time course	Poor prognosis	Spontaneous resolution

Taking all the data discussed above into account, the various results suggest that two types of inherent fast transporters can be distinguished: one related with co-morbidity and inflammation and another one related to mesothelial cell mass and/or function. The characteristics of these two types are shown in Table 7.1. The latter type is likely to disappear spontaneously with the duration of PD [32], because effluent CA 125 decreases during longitudinal follow-up [41, 50]. Although both types may cause ultrafiltration failure, the inherent fast transport status associated with CA 125 is unlikely to contribute to the excess mortality of fast transporters because most patients will have residual urine production. However, the type associated with co-morbidity and inflammation is likely to have a poor prognosis.

Acquired Fast Transporters

Here, two types can be distinguished. One occurs during peritonitis, the other one may develop during long-term PD. The characteristics are shown in Table 7.2.

Acute infectious peritonitis leads to an inflammation-induced peritoneal hyperemia. This causes some increase in peritoneal blood flow [51], but a much more marked increase of the transport of low molecular weight solutes [51, 52] and especially serum proteins [51–53]. It appeared that the changes in the parameters for the effective peritoneal vascular surface area were mediated by IL-6 and TNFα, while those for the intrinsic permeability of the peritoneum were associated with IL-6 and prostaglandin E2 [53]. The resulting decrease in ultrafiltration [51, 52] was purely due to a rapid decrease of the osmotic gradient, without signs of an impaired contribution of free water transport [54]. The vast majority of peritonitis episodes are cured by antibiotic treatment and peritoneal transport characteristics usually return to baseline in a few weeks [55].

Table 7.2 Differences between the two types of an acquired fast transport status

Acquired fast transporters		
	Associated with peritonitis	Associated with long-term PD
Vascular surface area increase	Effective	Anatomic
Cause	Infection	Glucose induced neoangiogenesis
Time course	Reversible after cure	Ultrafiltration failure

Patients on long-term peritoneal dialysis can develop ultrafiltration failure. This occurs in about one third of patients treated for 4–6 years [56, 57]. It is not only associated with a fast peritoneal transport status, but also with impaired free water transport [57–60]. Peritoneal neoangiogenesis induced by dialysis solutions is the main cause for this phenomenon [61–63]. It is also associated with low effluent CA 125 levels, suggesting extensive damage of the peritoneal dialysis membrane [57]. Most of the patients with this type of fast peritoneal transport status have no residual urine production. Therefore they are at great risk for the development of overhydration, which will lead to an increased mortality. Indeed, two studies performed in anuric patients have shown a relationship between peritoneal ultrafiltration and risk of death [64, 65].

Treatment of Patients with a Fast Transport Status

General principles of treatment include preservation of urine production and adjustments of the peritoneal dialysis prescription. Urine production can be preserved by avoidance of nephrotoxicity and the use of high-dose loop diuretics. The latter increase urine production, but have no effects on GFR [66] or its time course [67]. The use of an ACE inhibitor reduces the natural decline of residual GFR [68]. Modifications of the dialysis prescription consist of the use of icodextrin for the long dwell and/or the use of APD with short cycles. Two randomized studies showed that icodextrin treatment led to a significant reduction of total body and extracellular water and left ventricular mass [69, 70].

Specific treatment aimed at the cause of the fast peritoneal transport status is not always possible and also not always necessary. An inherent fast transport status associated with high effluent CA 125 levels requires no specific treatment. The condition is likely to disappear by itself. Treatment of the underlying condition of an inherent fast transport status associated with inflammation and/or co-morbidity should be attempted but is often impossible. This is especially the case for the malnutrition, inflammation, and arthrosclerosis syndrome, where an integrated approach should be investigated [71]. Prevention of the development of a fast transport status associated with long-term PD primarily consists of a reduction to the exposure to glucose and/or glucose degradation products [72]. The use of the so-called biocompatible PD solutions is promising in long-term animal models [73], but a sustained membrane protective effect in patients has not been established yet.

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